UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/688,198	10/17/2003	Gerardo Zapata	ABGENIX.057A	6664

20995 7590 02/27/2009

KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
BRISTOL, LYNN ANNE	

ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
02/27/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

jcartee@kmob.com
eOAPilot@kmob.com

Office Action Summary	Application No.	Applicant(s)	
	10/688,198	ZAPATA, GERARDO	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2008*.

2a)☒ This action is FINAL. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-11,13-23 and 25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5-11, 13-23 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-3, 5-11, 13-23 and 25 are all the pending claims for this application.

2. Claims 1, 7 and 19 are amended in the Response of 10/31/08.

3. Claims 1-3, 5-11, 13-23 and 25 are all the pending claims under examination.

4. Applicants amendments to the claims have necessitated new grounds for rejection. This Office Action is final.

.

Withdrawal of Rejections

Claim Rejections - 35 USC § 112, first paragraph

Enablement

5. The rejection of Claims 1-3, 5-11, 13-23 and 25 under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for culturing *antibody-producing cells* in a culture medium adjusted to about pH 3.5 and/or changed to any temperature in order to produce antibody fragments without affecting cell viability or the ability of the cells to produce antibody, is withdrawn.

Applicants have amended Claims 1, 7 and 19 to recite that it is not the cells that are pH adjusted or on which the temperature is changed, but the supernatants obtained from the cultured, antibody-producing cells.

New Grounds for Rejection

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-7, 10, 13 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by van Erp et al. (J. Biotechnol. 20:249-262 (1991); cited in the PTO 892 form of 11/26/07) as evidenced by Sigma data sheet for pepstatin A (3/19/01; cited in the PTO 892 form of 11/26/07).

Claims 1-7, 10, 11, 13 and 16 are interpreted as being drawn to producing any antibody fragment from any antibody produced or secreted into the cell culture medium by an antibody-producing cell by adjusting pH conditions of the media to activate at least one endogenous enzyme in order to cleave the antibody (Claim 1), cleaving antibodies into F(ab')2 fragments (Claim 2), further comprising adjusting the temperature conditions (Claim 3), adjusting the pH to about pH 3.5 (Claim 5), inactivating an enzyme (Claim 6), purifying the fragments by affinity chromatography (Claim 7), where the enzyme is aspartyl protease (Claim 10), the cell line is in protein-free media (Claim 13), and inactivating the enzyme by adjusting pH of the cultured medium (Claim 16).

van Erp discloses that mAbs produced by hybridomas undergo degradation by proteolytic enzymes (e.g., acid proteases) released by the cells to yield Ig fragments (p.

250, ¶2). Van Erp showed the highest degradation of IgG in serum-free medium at 37C occurred at pH 3 when the effect of adjusting pH on endogenous enzyme activity was measured (Figure 1) and proteolytic degradation was inhibited by pepstatin A (carboxyl protease inhibitor) (Table 1). As evidenced by Sigma catalog data sheet for peptstatin A, the inhibitor blocks aspartyl peptidases. van Erp purified acid proteases from hybridoma cells and mixed them with an IgG to observe proteolytic digestion patterns, where the digestion was compared to commercially prepared cathepsin D, and shown to produce similar results (p. 257, ¶3 to p. 258, ¶1; Figure 6). A 110k fragment was generated from IgG molecules which van Erp describes as a F(ab')2 like fragment observed by others (p. 260, ¶1). Van Erp teaches that the quantitative differences between the amounts of each fragment found in digestion experiments and serum-free culture supernatants might be explained by differences in enzyme concentrations and environmental factors such as culture medium but is certainly clone dependent (p. 260, ¶2). van Erp's disclosure is limited to pH adjustment of supernatant that does not contain any cells.

Comment [LAB1]:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. Claims 1-11, 13, 16-19, 21-23 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over van Erp et al. (J. Biotechnol. 20:249-262 (1991); cited in the PTO 892 form of 11/26/07) in view of Kratje et al. (J. Biotechnol. 32:107-125 (1994); cited in the PTO 892 form of 11/26/07) and Mason et al. (Protein Expression and Purification 23:45-54 (2001); cited in the PTO 892 form of 6/22/06) as evidenced by Sigma data sheet for pepstatin A (3/19/01; cited in the PTO 892 form of 11/26/07).

Claims 1-7, 10, 11, 13 and 16 are interpreted as being drawn to producing any antibody fragment from any antibody produced or secreted into the cell culture medium by an antibody-producing cell by adjusting pH conditions of the media to activate at least one endogenous enzyme in order to cleave the antibody (Claim 1), cleaving antibodies into F(ab')2 fragments (Claim 2), further comprising adjusting the temperature conditions (Claim 3), adjusting the pH to about pH 3.5 (Claim 5), inactivating an enzyme (Claim 6), purifying the fragments by affinity chromatography (Claim 7), where the enzyme is aspartyl protease (Claim 10), the cell line is in protein-free media (Claim 13), and inactivating the enzyme by adjusting pH of the cultured

medium (Claim 16). Claims 8, 9, 11, 17, 18 are interpreted as being drawn the method where the activated endogenous enzyme is a serine protease (Claim 8), or a cysteine protease (Claim 9), or where the cell line comprises a CHO cell line (Claim 11), or where inactivating the enzyme of Claim 16 comprises inactivating a cysteinyl enzyme (Claim 17), and where an aspartyl enzyme is activated by adjusting the pH after inactivating an endogenous cysteinyl enzyme (Claim 18).

Claim 19 is interpreted as being drawn to a method for producing F(ab')2 fragments comprising a cell media comprising expressing from an antibody-producing cell line inactivating endogenous cysteinyl enzyme activity in the cell media, and activating endogenous aspartyl enzyme activity in the cell media by adjusting the pH conditions of the cell media to produce F(ab')2 fragments. Claims 21-23 and 25 are interpreted as being drawn to inactivating endogenous cysteinyl enzyme activity of Claim 19 by adjusting the pH of the media (Claim 21) or by adding a cysteinyl enzyme inhibitor (Claim 22) and where the inhibitor is E64 (Claim 23), and the method comprising further purifying the F(ab')2 fragments (Claim 25).

The method of producing antibody fragments by activating endogenous enzymes in cell media from cultured antibody-expressing cells by adjusting the pH was prima facie obvious at the time of the invention over van Erp, Kratje and Mason as evidenced by Sigma data sheet.

van Erp discloses that mAbs produced by hybridomas undergo degradation by proteolytic enzymes (e.g., acid proteases) released by the cells to yield Ig fragments (p. 250, ¶2). Van Erp showed the highest degradation of IgG in serum-free medium at 37C

occurred at pH 3 when the effect of adjusting pH on endogenous enzyme activity was measured (Figure 1) and proteolytic degradation was inhibited by pepstatin A (carboxyl protease inhibitor) (Table 1). As evidenced by Sigma catalog data sheet for peptstatin A, the inhibitor blocks aspartyl peptidases. van Erp purified acid proteases from hybridoma cells and mixed them with an IgG to observe proteolytic digestion patterns, where the digestion was compared to commercially prepared cathepsin D, and shown to produce similar results (p. 257, ¶3 to p. 258, ¶1; Figure 6). A 110k fragment was generated from IgG molecules which van Erp describes as a F(ab')2 like fragment observed by others (p. 260, ¶1). Van Erp teaches that the quantitative differences between the amounts of each fragment found in digestion experiments and serum-free culture supernatants might be explained by differences in enzyme concentrations and environmental factors such as culture medium but is certainly clone dependent (p. 260, ¶2). van Erp's disclosure is limited to pH adjustment of supernatant that does not contain any cells. Van Erp does not explicitly teach the presence of serine proteases or cysteine proteases in cultured supernatants but appreciates that different cell clones could produce different proteases under different conditions which could affect antibody fragmentation depending upon the particular Mab (p. 250, ¶2). Kratje discloses that hybridoma cells produce cysteine and serine proteases under culture conditions.

Comment [LAB2]:

Krajte discloses the proteolytic capacities in serum-free hybridoma cell culture (murine hybridoma cell line 4/1-A) and the general cleavage potential of the proteases secreted in the culture supernantant (p. 108, Col. 2, ¶2). Krajte discloses through protease inhibition experiments using aprotinin (serine protease inhibitor), antipain

(papain and trypsin inhibitor; cysteine protease), PMSF (serine protease), SBTI (trypsin), and TPCK (trypsin and chymotrypsin) (p. 119, Col. 2, ¶1). Krajte specially teaches that the pH dependency of protease activation/inactivation is influenced by a) serum containing medium, b) cell specific conditions, and c) growth specific conditions, all of which would contribute to different observations (p.121, ¶1).

Neither van Erp or Krajte teach the cysteine protease inhibitor, E64, but Mason as evidenced by the Sigma data sheet teach that E64 is an art-recognized cysteine inhibitor that can be used to affect protease degradation of in culture medium.

One skilled in the art would have been motivated to have produced and been assured of reasonable success in having produced the instant claimed method based on the combined disclosures of van Erp, Kratje and Mason as evidenced by Sigma data sheet. At the time of the method invention, van Erp and Kratje specially taught and appreciated antibody fermentation technology and that depending on the antibody-producing cell, the growth media and the culture conditions, that proteases produced by the cultured cells could degrade the soluble antibodies into fragments, where van Erp in particular describes the generation of F(ab')2 fragments. Each of van Erp and Krajte demonstrate production of serine, cysteine and/or aspartyl proteases in the culture medium that are considered to produce a degradation effect depending on the antibody. Van Erp and Kratje examined the presence of proteases using protease inhibitors in culture supernatants for antibody-producing cells, and that the degradation products could be effected by modulating the proteases through pH adjustment as taught by van Erp and Kratje, temperature adjustment as taught by van Erp, inactivating proteases by

pH adjustment as taught by van Erp, or inactivating proteases by inhibitors as taught by van Erp, Kratje, Mason and as evidenced by Sigma data sheet. Further and based on van Erp's disclosure that in adjusting the pH at a temperature of 37C, one observes different degrees of IgG degradation, then absent a showing to the contrary, one skilled in the art could anticipate based on van Erp, that adjusting the pH could inactivate a cysteinyl enzyme while simultaneously activating an aspartyl enzyme according to instant Claim 19. One skilled in the art would have been reasonably assured of success in having produced the instant method because the knowledge of endogenous proteases in hybridoma-conditioned medium resulting in the formation of F(ab)2 fragments was already well established and that the conditions for manipulating the enzymes, e.g., changing pH and/or temperature and/or adding protease inhibitors, was already well characterized and well within the ordinary ability of the skilled artisan at the time of the invention. The manipulation of pH, temperature and/or addition of proteases to conditioned medium would not have required any more skills beyond those taught in the combined reference disclosures. Finally, the understanding that different clones and culture conditions could have produced different protease profiles and therefore would require different manipulation of the protease activity was already understood and appreciated by the combined reference disclosures.

8. Claims 1, 14, 15, 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over van Erp et al. (J. Biotechnol. 20:249-262 (1991); cited in the PTO 892 form of 11/26/07) in view of Kratje et al. (J. Biotechnol. 32:107-125 (1994); cited in the PTO 892 form of 11/26/07) as applied to claims 1 and 19 above, and further in view of Zhang et al (Cytotechnology 16:147-150 (1994); cited in the PTO 892 form of 6/22/06) and Schifferli et al. (Focus 21:16-17 (1999); cited in the PTO 892 form of 6/22/06). The interpretation of Claims 1 and 19 is discussed above under section 7. Claims 14 and 15 are drawn to the method of Claim 1 where the cell media is peptone source (Claim 14) or CH-CHO (Claim 15). Claim 20 is drawn to the method of Claim 19 where the cell media is CD-CHO.

The method of producing antibody fragments by activating endogenous enzymes in cell media from cultured antibody-expressing cells by adjusting the pH was prima facie obvious at the time of the invention over van Erp and Kratje in view of Zhang and Schifferli.

The interpretation of van Erp and Kratje alone and in combination is discussedabove under section 7. Neither reference specifically discloses the cell media of Zhang and Schifferli but each reference explicitly recognizes and discusses that culture conditions would effect the protease production of cultured cells resulting in fragmentation patterns that could vary for any given antibody-producing clone.

Zhang discloses that adding peptone to hybridoma medium can boost the level of antibody production and Schifferli discloses that CD-CHO medium is optimized for growth and expression of recombinant proteins by transfected cells.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced the instant claimed method over van Erp and Kratje in view of Zhang and Schifferli because increasing the level of antibody production by the antibody-producing cell line of the instant claimed method by optimizing the culture conditions using a peptone comprising medium of Zhang or the CD-CHO medium of Schifferli would have been well with ordinary skill at the time of the invention. One of ordinary skill would have been motivated to combine the media reagents into the methods disclosed by van Erp and Kratje in order to maximize antibody production in order to generate antibody fragments in usable amounts. Also, because these cell media reagents were commercially available, one could have readily obtained the materials at the time of the invention to incorporate into the method of van Erp and Kratje depending on the antibody-producing clone. One of skill in the art could have successfully combined the reagents into the methods of van Erp and Kratje as the media had been shown to be useful for expressing recombinant proteins including antibodies. Finally, the understanding that different culture conditions could have produced different protease profiles and therefore would require different manipulation of the protease activity to generate F(ab')2 fragments was already understood and appreciated by the combined reference disclosures.

Conclusion

9. No claims are allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LAB

/David J Blanchard/
Primary Examiner, Art Unit 1643